Depressive and Anxiety Symptoms in Patients With Schizophrenia and Schizophreniform Disorder

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Background: Symptoms of depression and anxiety are frequently encountered in the course of schizophrenia and are of considerable clinical importance. They may compromise social and vocational functioning, and they are associated with an increased risk of relapse and suicide. Various treatment approaches have been reported to be successful.

Method: The sample comprised 177 patients with DSM-III-R or DSM-IV schizophrenia or schizophreniform disorder who were participants in multinational clinical drug trials at our academic psychiatric unit over a 7-year period and who were assessed by means of the Positive and Negative Syndrome Scale (PANSS). Analysis was performed on baseline PANSS scores. The depression/anxiety score was compared in the men and women, first-episode and multiple-episode patients, and those with predominantly positive and negative syndromes. Correlations were sought between depression/anxiety scores and age, total PANSS score, positive score, negative score, general psychopathology score, and treatment outcome. Multivariate analysis was applied to determine contributions of individual variables toward depression/anxiety and outcome scores.

Results: Depression and anxiety symptoms were more severe in women ($p = .007$), first-episode patients ($p = .02$), and those with predominantly positive symptoms ($p < .0001$). Depression/anxiety scores were significantly correlated to age ($r = –0.31$, $p < .0001$), PANSS positive scores ($r = 0.39$, $p < .0001$), and treatment outcome ($r = 0.25$, $p = .006$). Multivariate analysis bore out these results, with the exception that first episode was not a significant predictor of depression and anxiety scores.

Conclusion: PANSS depressive/anxiety scores were generally low in our sample, perhaps because patients with schizoaffective disorder were excluded. The finding that these symptoms were more prominent in women and first-episode patients is in keeping with previous literature. The higher scores in first-episode patients are likely due to the higher positive symptom scores in these patients. The association between depressive/anxiety scores and positive symptoms but not with negative symptoms points to a specific relationship between affective symptoms and the positive symptom domain of schizophrenia. The presence of depressive and anxiety symptoms may predict a more favorable outcome to treatment, although this may only apply to the acute exacerbations of the illness.

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Symptoms of depression and anxiety are frequently encountered during the course of schizophrenia. They may occur during any phase of the illness and are not always easy to recognize. Depressive symptoms may mimic the negative symptoms of schizophrenia[1] and neuroleptic-induced akinesia, whereas anxiety symptoms may be indistinguishable from akathisia.[2,3] Possible causes of depression and anxiety in schizophrenia include response to adverse life events,[4] substance abuse,[1] comorbid major depression or anxiety disorders, neuroleptic-induced dysphoria,[5] or the possibility that these symptoms are a core feature of the schizophrenic illness.[6] The prevalence of depressive symptoms in schizophrenia has been reported as between 7% and 70%, depending on the criteria applied and populations studied.[7] Depressive symptoms are very common in first-episode schizophrenia,[6] the majority occurring concurrently with the psychotic symptoms and resolving as the psychosis remits. The majority of depressive symptoms appear to be related to the psychotic symptoms. Although the relationships are not clear-cut, the presence of depressive symptoms in the acute phase of the illness may be associated with a favorable outcome,[7,8] while in the chronic course they may be negative prognostic indicators.[9,10] Koreen et al.[6] found that depressive symptoms in their first-episode patients did not significantly affect the prognosis.

Anxiety symptoms in schizophrenia have been less well studied, although reports of comorbid anxiety disorders and syndromes, including obsessive-compulsive disorder,[11] panic attacks,[12] social anxiety disorder,[13] and posttraumatic stress disorder,[14] have appeared in the literature. Kay[15] found that depressive and anxiety symptoms clustered together as a distinct factor in patients with schizophrenia. Whatever their origins, depressive and anxiety symptoms in schizophrenia are of considerable clinical relevance. They may compromise social and vocational functioning and are associated with an increased risk of

relapse[16] and suicide.[17] The importance of recognizing these symptoms is further underlined by the fact that they may be responsive to various therapeutic interventions. Most depressive symptoms accompanying an acute psychosis resolve with neuroleptic treatment of the psychosis.[6] Tricyclic antidepressants, although not effective in treating depressive symptoms in actively psychotic patients,[18] were successful in treating postpsychotic depression,[19,20] as was lithium carbonate.[20] Decreased depression and suicidality was reported with clozapine treatment of neuroleptic-resistant schizophrenia.[21] More recently, olanzapine was found to be superior to haloperidol in reducing depressive signs and symptoms in schizophrenia, and this effect was independent of reduction of psychotic symptoms.[1] Alprazolam has been reported to be effective in schizophrenia with panic anxiety,[22] as has cognitive-behavioral therapy.[23]

This study further investigates depressive and anxiety symptoms in a large sample of patients with schizophrenia and schizophreniform disorder. The patients comprise participants in multinational clinical drug trials at our academic psychiatric unit (Cape Town, South Africa) who were assessed by means of the Positive and Negative Syndrome Scale (PANSS)[15] over a 7-year period.

METHOD

Patients meeting DSM-III-R[24] or DSM-IV[25] criteria for schizophrenia or schizophreniform disorder who had participated in multinational clinical trials within our department and in whom the PANSS had been used to assess symptom severity were included. All patients had provided informed, written consent to participate in the trials, and the studies were approved by the Ethics Committee of the University of Stellenbosch. The trials took place between 1991 and 1998 at an academic psychiatric hospital under a single principal investigator (R.A.E.). The other investigators were experienced psychiatrists who had undergone training and interrater reliability testing for using the PANSS. Subjects were aged between 18 and 65 years, had no concomitant significant medical conditions, and did not meet criteria for substance abuse. Schizoaffective disorder was an exclusion criterion for all of the trials.

Analysis was performed on baseline PANSS scores of all of the patients who had been randomly assigned to one of the trials. The following PANSS groups were selected, according to previously specified criteria[15]: total PANSS score (30 items); positive scale score (items P1–P7); negative scale score (items N1–N7); composite score (positive scale score minus negative scale score); and general psychopathology scale score (items G1–G14). Patients were also divided into those with predominantly positive syndromes (score of 4 or more on at least 3 of the positive items and on fewer than 3 on the negative scale) and those with predominantly negative syndromes (score of 4 or more on at least 3 of the negative items and on fewer than 3 on the positive scale), and into those suffering from their first psychotic episode and those suffering from recurrent psychotic episodes. Depressive and anxiety symptoms were examined in these different groups. The depression/anxiety factor comprised the sum of the scores from PANSS items G1 (somatic concern), G2 (anxiety), G3 (guilt feelings), and G6 (depression). Finally, correlations were sought between depression/anxiety scores and the following variables: age, total PANSS score, positive score, negative score, general psychopathology score, and treatment outcome as assessed by the change from baseline in total PANSS scores (minus depression/anxiety items) at 6 weeks (or the closest assessment to 6 weeks, ranging from weeks 5 through 9).

Statistical Analysis

The Student t test (2-tailed) and the Pearson product moment correlation coefficient were used for differences and correlations between numeric variables. To determine the contributions of individual variables toward depression/anxiety and outcome scores, significant univariate results were followed with regression analysis with simultaneous entry, using the method of least squares. The significance level was set at .05.

RESULTS

The sample comprised 177 subjects, of whom 113 (64%) were men and 64 (36%) women. The mean ± SD age was 35.6 ± 13.36 years. Sixty (34%) were first-episode patients. The median number of psychotic episodes in the multiple-episode group was 2 (interquartile range = 3). DSM diagnoses were as follows: paranoid schizophrenia (N = 41), disorganized schizophrenia (N = 28), catatonic schizophrenia (N = 2), undifferentiated schizophrenia (N = 50), residual schizophrenia (N = 27), and schizophreniform disorder (N = 29). For the entire sample, mean ± SD PANSS scores were as follows: positive scale score = 20.5 ± 6.82; negative scale score = 24.5 ± 6.71; general psychopathology scale score = 38.6 ± 9.06; total PANSS score = 83.6 ± 17.61; composite score = –4.0 ± 9.66; and depression/anxiety factor = 7.8 ± 3.05.

We were initially interested in looking at anxiety and depressive symptoms separately. To determine whether these were in fact separate entities, we selected the items that we considered to represent "pure" anxiety (G2 [anxiety] + G4 [tension]) and depressive (G3 [guilt feelings] + G6 [depression]) symptoms and correlated them. A highly significant correlation ($r = 0.5$, $p < .0001$) was found between these factors, indicating that depression and anxiety symptoms largely occurred together in our sample of patients. This is in keeping with the original

Table 1. PANSS Scores (mean ± SD) for Men and Women With Schizophrenia or Schizophreniform Disorder[a]

PANSS Score	Men (N = 113)	Women (N = 64)	p Value
Depression/anxiety	7.29 ± 2.95	8.6 ± 3.09	.007
Positive	20.4 ± 6.70	20.8 ± 7.08	NS
Negative	24.7 ± 7.25	24.2 ± 5.68	NS
General psychopathology	38.3 ± 8.75	39.1 ± 9.62	NS
Total	83.4 ± 17.07	84.1 ± 18.65	NS
Composite	–4.3 ± 10.45	–3.4 ± 8.14	NS

[a]Abbreviations: NS = not significant, PANSS = Positive and Negative Syndrome Scale.

Table 2. PANSS Scores (mean ± SD) for First-Episode and Multiple-Episode Patients With Schizophrenia or Schizophreniform Disorder

PANSS Score	First Episode (N = 60)	Multiple Episode (N = 115)	p Value
Depression/anxiety	8.5 ± 3.32	7.4 ± 2.84	.02
Positive	23.7 ± 5.15	18.7 ± 6.94	< .0001
Negative	23.3 ± 8.06	25.3 ± 5.79	.05
General psychopathology	41.4 ± 10.19	37.2 ± 8.08	.003
Total	88.4 ± 19.2	81.2 ± 16.33	.01
Composite	0.42 ± 9.24	–6.5 ± 8.89	< .00001

principal component analysis of Kay,[15] in which the depressive and anxiety symptoms of the PANSS scale formed a single component. We therefore examined depression and anxiety symptoms as one factor, using the items identified by Kay[15] (G1, G2, G3, and G6). Table 1 shows the various PANSS scores for men and women, and Table 2 shows the various PANSS scores for first-episode and multiple-episode patients. Thirty-four patients met criteria for a predominantly positive syndrome, and 59 for a predominantly negative syndrome; the mean ± SD depression/anxiety scores for these 2 groups were, respectively, 8.2 ± 2.5 and 6.3 ± 2.4. The difference between these groups was highly significant ($p = .0004$). The depression/anxiety score was found to correlate significantly with age ($r = –0.31$, $p < .0001$), PANSS positive score ($r = 0.39$, $p < .0001$), and treatment outcome ($r = 0.25$, $p = .006$), but not with the PANSS negative score ($r = –0.07$, $p = .4$).

Because the depression/anxiety factor was related to both first episode and positive symptom scores, and first-episode patients had significantly higher positive symptom scores, multiple regression, using the method of least squares, was performed. The depression/anxiety score was the dependent variable, and age, sex, first episode, positive score, negative score, and the interaction of positive score and first episode were the independent variables. The overall regression was significant ($F = 8.54$, $df = 6,168$; $p < .0001$; adjusted $R^2 = 0.21$), suggesting that 21% of the variance in depression/anxiety scores was associated with the model. Significant predictors were younger age ($p = .02$), female gender ($p = .005$), and positive symptoms ($p = .04$).

To identify the contributions of age, sex, first episode, and depression/anxiety score to predicting outcome, multiple regression was performed with outcome as the dependent variable and the other variables as predictor variables. The symptoms included in the depression/anxiety factor (G1, G2, G3, and G6) were excluded from the total PANSS scores. The overall regression was significant ($F = 4.46$, $df = 4,117$; $p < .002$; adjusted $R^2 = 0.10$), suggesting that 10% of the variance in outcome could be explained by these variables. The only significant predictor was depression/anxiety score ($p = .04$).

DISCUSSION

The major findings of this study were that depressive and anxiety symptoms were more prominent in women, those with predominantly positive symptoms, and those suffering from their first psychotic episode. A significant negative association was found with age, and a significant positive association was found with positive symptoms. Generally, symptoms of depression and anxiety were present only to a moderate degree, even in the first-episode patients. This is in contrast to the findings of Koreen et al.[6] (although direct comparisons are not possible because different scales were used to assess symptom severity). This discrepancy could be due to the fact that patients with schizoaffective disorder were excluded from our sample.

The finding that depressive and anxiety symptoms are more prominent in women is in keeping with previously reported gender differences in schizophrenia.[26] Bardenstein and McGlashan,[27] after reviewing the literature, concluded that women with schizophrenia are more likely to experience affective symptoms, whereas men are likely to have more prominent negative symptoms. Häfner et al.[28] found more depressive symptoms in women than in men in first-admission patients with schizophrenia. However, it is possible that these results could reflect differences in men and women that are not related to schizophrenia.[28] Also, the differences, although significant, are small and may not be clinically meaningful.

As did the studies by House et al.[29] and Koreen et al.,[6] our study showed that depressive and anxiety symptoms were more prominent in patients experiencing their first episode of schizophrenia. Again, however, the differences, although significant, are small and may not have clinical relevance. On the other hand, the additional clear-cut differences between first-episode and multiple-episode patients regarding positive symptoms, negative symptoms, and general psychopathology scores indicate that the psychopathology of first-episode schizophrenia is different from that of multiple-episode schizophrenia. Multivariate analyses indicate that the higher positive symptom scores in first-episode patients most likely account also for the higher levels of depressive and anxiety

symptoms encountered in first-episode compared with multiple-episode patients.

Whereas Koreen et al.[6] found depression to be significantly correlated with both positive and negative symptoms, we found a significant correlation with positive symptoms only. Our findings are thus consistent with other studies[30,31] in indicating an association between depression/anxiety and positive symptoms, with independence of negative symptoms. These results point to a specific association between these affective symptoms and the positive symptom domain of schizophrenia. There are several possible explanations for this association. First, it could be that depressive and anxiety symptoms are secondary to the positive symptoms. Second, in the stress-diathesis context, these affective symptoms may themselves constitute a stressor that triggers a psychotic episode.[32] Third, affective symptoms and positive symptoms may represent common clinical manifestations of the same underlying pathologic process. This latter possibility is consistent with the proposal that depression is a core part of schizophrenia that occurs at the height of psychosis and decreases over the course of treatment.[6]

The finding that depression and anxiety scores correlated with treatment response is consistent with that reported by Kay,[15] who found that this factor emerged as the only clinical variable to reliably predict good outcome. This is particularly interesting considering that both our study and that of Kay excluded patients with schizoaffective disorder. Thus, the better prognosis in patients with schizophrenia with affective symptoms cannot be explained on the basis that these patients were actually suffering from schizoaffective disorder. However, the fact that most of our patients were experiencing acute exacerbations of their illness is consistent with other studies indicating that the favorable outcome associated with depressive symptoms may only apply to the acute phase of the illness.[7,8]

There are a number of limitations to this study. Firstly, we only looked at symptoms of depression and anxiety and not at specific comorbid mood and anxiety disorders. Secondly, side effects of medication taken prior to the onset of the trials were not assessed. Although patients had undergone a washout period of 3 to 7 days before the PANSS assessment was done, extrapyramidal or other side effects from previously taken medication could have influenced the results. However, medication effects are unlikely to have played a major role, considering that previous studies failed to show a strong association between depression and extrapyramidal symptoms.[6,29] Thirdly, the various investigators may have rated symptoms differently. The fact that regular interrater reliability training took place, and the same principal investigator was present for all of the studies, decreases the likelihood of this possibility. Finally, the correlations with treatment outcome need to be interpreted with caution, since patients obviously received different treatments. Details of medication were not available to us, since a number of the studies had not been unblinded at the time of our analysis.

In conclusion, the assessment of depressive and anxiety symptoms in patients with schizophrenia is of considerable importance. These symptoms may be core features of the illness and may be of value in predicting the treatment outcome in patients suffering from acute exacerbations of the illness.

Drug names: alprazolam (Xanax and others), clozapine (Clozaril and others), haloperidol (Haldol and others), olanzapine (Zyprexa).

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